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(54) Title: COMBINATION THERAPY FOR ERADICATING DETECTABLE HCV-RNA IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION (57) Abstract <p>There is disclosed the use of ribavirin, interferon alpha or a combination of ribavirin and interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy. The compositions may be used in a method for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA involving a combination therapy using a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of from 20 up to 80 weeks.</p>		

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**COMBINATION THERAPY
FOR ERADICATING DETECTABLE HCV-RNA
IN PATIENTS HAVING CHRONIC HEPATITIS C INFECTION**

Chronic infection with hepatitis C virus is an insidious and slow-progressing disease having a significant impact on the quality of life. It can eventually result in cirrhosis of the liver, decompensated liver disease and/or hepatocellular carcinoma.

Interferon alpha monotherapy is commonly used to treat chronic hepatitis C infection. However, this treatment is not always effective and sometimes results in intolerable side effects related to the dosage and duration of therapy. Ribavirin has been proposed as a monotherapy treatment for chronic hepatitis C infection (Thomas et al. AASLD Abstracts, Hepatology Vol. 20, NO. 4, Pt 2, Number 440, 1994). However, this monotherapy treatment has usually been found relatively ineffective and has its own undesirable side effects. Combination therapy of interferon alpha and ribavirin has been proposed (Lai, et al. Symposium to the 9th Biennial Scientific Meeting Asian Pacific Association for the Study of the Liver. 1994). Preliminary results suggest that the combination therapy may be more effective than either monotherapy. Hayden FG, Schlepishkin AN. Combined interferon-2a, rimantadine hydrochloride, and ribavirin inhibition of influenza virus replication *in vitro*. *Antimicrob Agents Chemother*. 1984;25:53-57. Schvarcz R, Ando Y, Sannerborg A, Weiland O. Combination treatment with interferon alfa-2b and ribavirin for chronic hepatitis C in patients who have failed to achieve sustained response to interferon alone: Swedish experience. *J Hepatology*. 1995;232 (Suppl 2):17-21. Brouwer JT, Nevens F, Michielsen P, et al. What options are left when hepatitis C does not respond to interferon? Placebo-controlled Benelux multicentre retreatment trial on ribavirin monotherapy versus combination with interferon. *J Hepatol*. 1994;212 (Suppl 1):S17. Abstract WP2/08. Chemello L, Cavalletto L, Bernardinello E, et al. Response to ribavirin, to interferon and to a combination of both in patients with chronic hepatitis C and its relation to HCV genotypes. *J Hepatol*. 1994;212 (Suppl 1):S12. Abstract GS5/29.

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However, no one has described methods using interferon alpha and ribavirin which eradicate HCV-RNA in any long-term, effective manner.

There is a definite need for a method for treating chronic hepatitis C
5 infection with a combination of interferon alpha and ribavirin which eradicates HCV-RNA in any long-term, effective manner.

SUMMARY OF THE INVENTION

10 According to one aspect of the invention, there is provided the use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in
15 association with an effective amount of interferon alpha, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy.

According to another aspect of the invention, there is provided the use
of interferon alpha for the manufacture of a pharmaceutical composition for
20 treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of interferon alpha in association with an effective amount of ribavirin, wherein the patient is one having failed to respond to a previous course of interferon
alpha therapy.

25 The invention further provides the use of both ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in
30 association with an effective amount of interferon alpha, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy.

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The pharmaceutical compositions are of particular utility for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 20 to 30 weeks, such that at least about 30% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

Preferably, at least about 40% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

In another embodiment they may be used for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 40 to 50 weeks, such that at least about 40% of the patients having no detectable HCV-RNA at the end of said 40 to 50 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

Preferably, at least about 50% of the patients having no detectable HCV-RNA at the end of said 40 to 50 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

In another embodiment they may be used for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 60 to 80 weeks, such that at least about 50% of the patients having no detectable HCV-RNA at the end of said 60 to 80 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

Preferably, at least about 60% of the patients having no detectable HCV-RNA at the end of said 60 to 80 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

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In another embodiment they may be used for treating a patient having chronic hepatitis C infection having HCV genotype other than type 1 and having a viral load of less than or equal to 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 20 to 30 weeks, such that at least about 60% and preferably at least about 70% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration. Preferably, at least about 80% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

In another embodiment they may be used for treating a patient having chronic hepatitis C infection having HCV genotype other than type 1 and having a viral load of greater than 2 million copies as measured by HCV-RNA/qPCR to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 20 to 30 weeks; such that at least about 50% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration. Preferably, at least about 60% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

In another embodiment they may be used for treating a patient having chronic hepatitis C infection having HCV genotype type 1 and having a viral load of less than or equal to 2 million copies as measured by HCV-RNA/qPCR to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 20 to 30 weeks, such that at

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least about 30% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration. Preferably, at least about 40% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

In another embodiment they may be used for treating a patient having chronic hepatitis C infection having HCV genotype type 1 and having a viral load of greater than 2 million copies as measured by HCV-RNA/qPCR to eradicate detectable HCV-RNA comprising administering a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of 20 to 30 weeks, such that at least about 15% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration. Preferably, at least about 20% of the patients having no detectable HCV-RNA at the end of said 20 to 30 week period also have no detectable HCV-RNA for at least 24 weeks after the end of said administration.

Preferably, the amount of ribavirin administered is from 400 to 1200 mg per day. More preferably, the amount of ribavirin administered is from 800 to 1200 mg per day.

The interferon-alpha administered is preferably selected from interferon alpha-2a, interferon alpha-2b, a consensus interferon, a purified interferon alpha product or a pegylated interferon-alpha. More preferably, the interferon-alpha is selected from interferon alpha-2a, interferon alpha-2b, or a purified interferon alpha product and the amount of interferon-alpha administered is from 2 to 10 million IU per week on a weekly, TIW, QOD or daily basis. In a preferred embodiment, the interferon-alpha administered is interferon-alpha-2b and the amount of interferon-alpha is administered 3 million IU TIW.

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Alternatively, the interferon-alpha administered is consensus interferon and the amount of interferon-alpha administered is from 1 to 20 micrograms per week on a weekly, TIW, QOD or daily basis. In another embodiment, the
5 interferon-alpha administered is a pegylated interferon alpha-2b and the amount of interferon-alpha administered is from .5 to 2.0 micrograms/kilogram per week on a weekly, TIW, QOD or daily basis. Alternatively, the interferon-alpha administered is a pegylated interferon alpha-2a and the amount of interferon-alpha administered is from 20 to 250
10 micrograms/kilogram per week on a weekly, TIW, QOD or daily basis.

The present invention has surprisingly found that, when compared to interferon-alpha treatment alone or ribavirin alone, therapy with a combination of a therapeutically effective amount of ribavirin and a therapeutically effective
15 amount of interferon-alpha for a time period of at least 20 to 30 weeks results in ten times more patients having no detectable HCV-RNA in their serum at least 24 weeks after termination of therapy than by either monotherapy.

DETAILED DESCRIPTION

20

The term "interferon-alpha" as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon alphas include, but are not limited to, recombinant interferon alpha-2b such
25 as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alpha-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of
30 natural alpha interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus interferon alpha such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples

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7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alpha-n3 a mixture of natural interferon alphas made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alpha-
5 2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

10 Ribavirin, 1- -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

15 By 'failed to respond to a previous course of treatment' is meant that the patient either failed to respond to a previous course of treatment at all (generally termed in the art 'non-responder') or that the patient responded to a previous course of treatment but then subsequently relapsed (generally termed in the art 'non-sustained responder').

20 By 'difficult to treat patient' is meant a patient that heretofore has been classified as one not readily responding to treatment; for instance because of high viral load or because the HCV infection is a difficult to treat genotype such as type 1, for example type 1b. For further details of the classification of
25 HCV into separate genotypes, see, e.g. "Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region", Simmonds, P. *et al.*, J. Gen Virol.(1993), 74, 2391-2399 and "A Proposed System for the Nomenclature of Hepatitis C Viral Genotypes", Simmonds, P. *et al.*, Hepatology, 19(5) (1994), 1321-1323.

30 A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

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(a) elevated ALT,

(b) positive test for anti-HCV antibodies,

5 (c) presence of HCV as demonstrated by a positive test for HCV-RNA,

(d) clinical stigmata of chronic liver disease,

(e) hepatocellular damage.

10

To practice the invention, interferon alpha (hereinafter α -IFN) and ribavirin are administered to the patient exhibiting one of more of the above signs or symptoms in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms. In a preferred embodiment, the
15 combination therapy of the invention is administered to a patient who has failed to remain HCV-RNA free after interferon-alpha monotherapy.

The ribavirin is administered to the patient in association with the α -IFN, that is, the α -IFN dose is administered during the same period of time
20 that the patient receives doses of ribavirin. Most α -IFN formulations are not effective when administered orally, so the preferred method of administering the α -IFN is parenterally, preferably by subcutaneous, IV, or IM, injection. The ribavirin may be administered orally in capsule or tablet form in association with the parenteral administration of α -IFN. Of course, other types of
25 administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

30

Detectable HCV-RNA in the context of the present invention means that there is less than 100 copies per ml of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA

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is preferably measured in the present invention by the methodology described below. This methodology is referred to herein as HCV-RNA/qPCR.

RNA is extracted from patient serum using a guanidinium thiocyanate-phenol-chloroform mixer followed by ethanol-ammonium acetate precipitation. The precipitated RNA is centrifuged and the resulting pellet is dried in a Centrivap console (Labconco, Kansas City, Mo.). The dry pellet is then resuspended in 30 microliters of an Rnasin (Promega Corp., Madison, WI), dithiothritol, and diethylpyrocarbonate-treated water mixture. Samples are kept at or below -20 C until RNA reverse transcription (RT) and PCR.

In order to convert the entire RNA sequence into cDNA in the RT reaction, random hexadeoxyribonucleotides (Pharmacia Biotech, Piscataway, NJ) are used as primers for the first strand cDNA synthesis. Two aliquots of 3 microliters of resuspended sample is added to 3 microliters of 100ng/ l random primers and denatured at 70 C, then reverse transcribed at 40 C for one hour using M-MLV reverse transcriptase (USB, Cleveland, OH) in standard buffer containing 5 mM MgCl₂. The final RT reaction volume is 26 l. The PCR is started immediately following the reverse transcription.

A modified version of the PCR method is performed using heat-stable Taq polymerase to amplify the cDNA. Seventy-five microliters of PCR mix is added to the entire RT reaction volume (26 l) to a final MgCl₂ concentration of 1.5 mM in a total volume of 101 l. Each 101 l sample is then split into 50.5 l, and a layer of mineral oil is placed on top to prevent evaporation.

The PCR cycle consists of annealing for 90 sec., extension for 90 sec., and denaturation for 90 sec., at 55 C, 74 C and 94 C, respectively. Thermocycling samples is submitted to a final 74 C extension for 10 minutes. Four different cycle sets are used. By loading the sample in duplicate, and splitting these samples evenly after RT, there are four tubes from one sample. Each of the four tubes is given a different cycle number, enhancing sensitivity and accuracy in the quantitation process. The thermocycling

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efficiency will be assessed by satisfactory amplification of known copy number RNA standards included in each set of 60 tubes. Two primer sets are used for the amplification, both from the 5' untranslated region of the HCV genome. Both of these primer sets are highly conserved and detect all
5 known subtypes of HCV. Primer set 1: upstream 5' -GTG GTC TGC GGA ACC GGT GAG T-3', downstream 5'-TGC ACG GTC TAC GAG ACC TC-3' which produced a 190 bp product. Primer set 2: upstream 5'-CTG TGA GGA ACT ACT GTC TTC-3', downstream 5'-CCC TAT CAG GCA GTA CCA CAA-3' which produced a 256 bp product.

10

The amplified cDNA is then electrophorised in 3% agarose gel and transferred to nylon membrane. The target DNA is detected by Southern blotting and immunostaining using a nonradioactive digoxigenin-labeled DNA probe. These procedures are performed using automated instruments
15 for PCR thermocycling, agarose gel electrophoresis, vacuum-transfer Southern blot, hybridization, and immunostaining. Each membrane contains known copy number serially diluted standards which are used to construct standard curves for quantitative measurement of the specimen bands.

Originally standard curves are made from carefully diluted HCV-RNA from
20 transcribed clones. Radioactive incorporation studies, gel electrophoresis, and OD 260 are performed on the transcripts to determine that they are of the expected length. After the production of the RNA transcripts quantitated clone standards "pooled" standards are generated which better represent the heterogeneous nature of HCV, one would encounter in natural infection.

25 These pools are made by combining large amounts of serum or plasma from known infected individuals. The serum/plasma pools are calibrated with PCR, against the clone transcripts and then diluted in the known PCR-negative fluids. Finally, the higher copy number samples of the pools are checked against the cDNA Quantiplex nucleic acid detection system from
30 Chiron Inc. (Emeryville, CA). These "double quantitated" pools are aliquoted and saved at -70 C. Dilutions of 5,000,000, 1,000,000, 500,000, 100,000, 10,000, and 1000 copies/ml are used in each experiment.

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Each Southern blot membrane is scanned into a computer using an automated scanner/densitometer, at intervals during development to determine when the standard curve is most linear. The resultant electronic images are then measured for band area and mean band density. All of the reading are standardized to integrated band density and compared to the standard curve to obtain a numerical value of viral copy number for each band.

The following clinical protocols were performed:

Study 1:

Overall Design and Plan of the Study

This was a prospective, multicenter, randomized, double-blind, parallel-group. The study compared treatment with INTRON® A plus ribavirin to treatment with INTRON® A plus placebo for 24 weeks in patients with compensated chronic hepatitis C who had responded to one or two previous courses of interferon alpha (INTRON® A, Roferon®-A, or Wellferon®) therapy (minimum of 3 MU to a maximum of 6 MU QOD or TIW for a minimum of 20 weeks to a maximum of 18 months) and who had relapsed after the most recent course of interferon alpha therapy. Eligible patients had chronic hepatitis C confirmed by positive serum HCV-RNA, liver biopsy, and laboratory tests.

Patients were randomized to treatment with either INTRON® A plus ribavirin or INTRON® A plus placebo. The dose of INTRON® A was 3 MU SC TIW; the dose of ribavirin was 1000 or 1200 mg PO daily (based on weight) in two divided doses. Treatment group assignments were made in equal ratios by a Central Randomization Center. The randomization procedure was designed to attempt to balance the treatment groups, within and across sites, with respect to presence or absence of cirrhosis in the pretreatment liver biopsy, serum HCV-RNA/qPCR level, and HCV genotype.

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Study treatment was administered for 24 weeks. The total course of the study was 48 weeks to determine long-term effect of treatment.

During treatment and posttreatment follow-up, biochemical (ALT),
5 virological (HCV-RNA), and histological (liver biopsy) examinations were used to assess the nature and duration of response to study treatment. The primary efficacy variable was the overall response defined as loss of serum HCV-RNA/qPCR (<100 copies/mL) as measured at 24 weeks following the end of therapy associated with an improvement in posttreatment liver biopsy
10 as measured by the Knodell Histology Activity index (HAI). Normalization of ALT was also examined as a secondary efficacy variable. The safety of the study treatments was assessed by monitoring selected laboratory parameters and by also recording and evaluating the occurrence of any adverse events.

Treatment Regimens

20 The study treatment regimens were either:

- INTRON® A 3 MU SC TIW plus ribavirin 1000 or 1200 mg/day
25 PO in two divided doses for 24 weeks ; or
- INTRON® A 3 MU SC TIW plus placebo matching ribavirin PO in two divided doses for 24 weeks.

Study treatment was administered for 24 weeks. The standard INTRON® A
30 (interferon alfa-2b, recombinant) regimen for hepatitis C was administered as a fixed dose of 3 MU TIW. Each patient received instructions regarding the preparation and subcutaneous administration of INTRON® A. Ribavirin was administered twice daily, morning and evening. The dose was determined by the patient's body weight at the Entry visit. Patients weighing =75 kg received
35 1000 mg daily as two 200 mg capsules in the morning and three 200 mg capsules in the evening. Patients weighing >75 kg received 1200 mg daily

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as three 200 mg capsules morning and evening.

The randomization procedure was designed to balance the groups with respect to the following Baseline characteristics:

- 5 A.pretreatment liver histology (cirrhosis or no cirrhosis);
- B.serum HCV-RNA/qPCR status (HCV-RNA/qPCR \leq 2,000,000 or HCV-RNA/qPCR $>$ 2,000,000 copies/mL); and
- C.HCV Genotype (1 or other). Patients with mixed genotypes (which include Type 1) will be classified as Type 1 for purposes of
- 10 balancing.

Efficacy

The primary efficacy objective was comparison of the two treatment groups with respect to the overall response rate defined as loss of serum HCV-RNA/qPCR at 24 weeks following the end of therapy to an undetectable level or to a level $<$ 100 copies/mL associated with an improvement in Post treatment liver biopsy as defined by the Knodell HAI inflammation score. The following secondary efficacy Endpoints were also examined:

The secondary efficacy Endpoints:

- 20 D.proportions of patients with normalization of ALT at 24 weeks of follow-up;
- E.proportions of patients with improvement in biopsy (Categories I + II +III combined scores);
- F.changes from Baseline in the biopsy scores (Categories I + II + III combined scores);
- 25 G.response rates at Endpoint of treatment based on HCV-RNA/qPCR;
- H.proportion of patients with normalization of ALT at Endpoint of treatment.
- 30 I.response rates at 24 weeks of follow-up based on HCV-RNA/qPCR.

Virology: Entry Status and Change from Entry

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Serum HCV-RNA/qPCR testing was performed by a central laboratory. A positive HCV-RNA assay result was required at Baseline; only patients positive for HCV-RNA were eligible to participate. Repeat assays were scheduled at Weeks 4, 12, 24, and Follow-up Weeks 12 and 24.

5 Response was assessed as defined below:

Responder: A patient was classified as a responder at a given time point if HCV-RNA/qPCR was negative (<100 copies per mL) at that time point.

10 **Sustained Responder:** A patient was classified as a sustained responder if the patient was a responder at 24 weeks of follow-up.

Note that patients who do not meet these criteria, including patients who discontinued before the required HCV-RNA/qPCR evaluations were obtained,
15 were classified as non-responders.

Overall Responder: Based on both serum HCV-RNA/qPCR and change in liver histology as evaluated by the Knodell HAI Inflammation Score. A patient was classified as an overall responder to treatment if
20 he/she was a sustained responder and his/her Post treatment Knodell HAI inflammation score (sum of categories I+II+III) improved by 2 or more units relative to the Pretreatment score.

25 Liver Histology

Liver biopsy was required within the six months preceding patient enrollment and at Follow-up Week 24. Evaluation of the biopsies was performed by a single pathologist using the Knodell Histology Activity Score.
30 The central pathologist was blinded with respect to patient identification, treatment group, and the time the biopsy was obtained relative to treatment (Pre- or Posttreatment). Efficacy of study treatments was assessed by comparing the degree of inflammatory activity observed at Baseline with that present at Follow-up Week 24.

35

RESULTS

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One hundred-ninety-five patients were enrolled at 31 international centers and randomized to treatment with either INTRON® A plus ribavirin (N=98) or INTRON® A plus placebo (N=97). Three patients, two randomized to receive INTRON® A plus ribavirin and one randomized to receive INTRON® A plus placebo were not treated; thus, the all-treated groups consisted of 192 patients (96 patients each for INTRON® A plus ribavirin and INTRON® A plus placebo). Two of the three patients were not treated because they did not wish to continue, the third because the protocol criteria were not met. All discussions of efficacy and safety in this report are based on data for the all-treated groups.

Efficacy

The objectives of this study were to compare INTRON® A plus ribavirin with INTRON® A plus placebo with respect to the overall response rate and the virologic response rate (based on HCV-RNA (qPCR)). The primary efficacy variable for the study is the overall response rate.

The conclusion from this regarding efficacy are as follows:

J. Combining ribavirin with INTRON® A can dramatically increase the proportion of patients who eradicate HCV-RNA and have significant reduction in hepatic inflammation.

The End of Follow-up overall response rate is a composite of the loss of serum HCV-RNA (qPCR) and change in liver histology at end of follow-up (24 weeks following the end of treatment). A patient was classified as an overall responder if HCV-RNA (qPCR) was negative at the 24 week posttreatment evaluation and the posttreatment Knodell HAI inflammation score (sum of categories I+II+III) had improved by 2 or more units relative to the pretreatment score. The End of Follow-up virologic response, histologic response, and overall response rates are summarized in Tables 1, 2, and 3.

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End of Follow-up HCV-RNA Response: Sustained Loss of HCV-RNA
24 Weeks Following the End of Treatment

5 The proportion of patients with eradication of HCV-RNA in the serum
24 weeks following the end of treatment was tenfold greater ($p < 0.001$) in the
group of patients treated with the combination of INTRON® A plus ribavirin
compared to those receiving INTRON® A monotherapy. Table 1 summarizes
the End of Follow-up patient response as indicated by serum HCV-RNA.

Table 1 End of Follow-up Serum HCV-RNA: Proportion of Patients with Eradication of
HCV-RNA at 24 Weeks Following the End of Treatment.

Patient Response Status	Number (%) of Patients		p value
	INTRON® A plus Ribavirin	INTRON® A plus Placebo	
All Treated	50/96	5 /96 (5)	<0.001
95% Confidence Interval	(52)		
for each treatment:		1%-10%	
	4%-58%		
for difference between	42%-62%		
treatments:			
Responders at End of	49/80	5/41 (12)	
Treatment ^c	(61)		

10

15 Pre- and Posttreatment biopsies were available for 81% (78/96) of the
patients treated with INTRON® A plus ribavirin and for 77% (74/96) of those
patients who received INTRON® A plus placebo. Table 2 summarizes the
effect of treatment on hepatic inflammation for patients with both pre- and
posttreatment liver biopsy results. As with the sustained loss of HCV-RNA
replication, the proportion of patients with improvement in liver inflammation
was significantly greater ($p < 0.001$) in patients receiving combination therapy
compared to those receiving INTRON® A monotherapy.

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Table 2 End of Follow-up Liver Histology: Improvement in Liver Histology 24 Weeks Following the End of Treatment Based on the Knodell HAI (I+II+III) Score.

Patient Status	Number (%) of Patients ^b		p value ^c
	INTRON A plus Ribavirin (n=78)	INTRON A plus Placebo (n=74)	
Improved Biopsy ^d	49 (51)	30(31)	<0.001

^b Patients with both pre- and posttreatment biopsy.

^c Fisher's Exact test.

^d Change from pretreatment to posttreatment in the Knodell Histological Index (HAI) score (sum of I+II+III) categorized as a decrease of 2 or more from pretreatment.

Overall Response

5

When the study was designed, it was recognized that because liver biopsy is an invasive procedure that it would be unlikely that posttreatment liver biopsies would be obtained for all patients. Therefore, the protocol and statistical analysis plan specified that the analysis for overall response would be based on data for all treated patients and will be estimated by a maximum likelihood method (MLE) for patients whose overall response status could not be determined, ie, patients with negative HCV-RNA and missing (posttreatment) biopsy evaluations. The protocol also specified that an additional analysis would be performed on patients with both pretreatment and posttreatment biopsy results (ie, patients with complete data). The overall response is summarized in **Table 3** based on the following analyses:

- K.maximum likelihood estimate (MLE);
- L.patients with complete data (results for both pre- and posttreatment biopsy);
- M.patients with missing data (either or both HCV/biopsy) treated as failures.

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Table 3 Overall Response Rate.

Data Analyzed	INTRON® A plus Ribavirin	INTRON® A plus Placebo	p value ^b
Maximum likelihood estimate	43%	5%	<0.001
Patients with complete data ^c	39/78 (50%)	4/74 (5%)	<0.001
Treat missing as failures ^d	39/96 (41%)	4/96 (4%)	<0.001

1. MLE based on logistic regression

1. Fisher's exact test.

1. Complete data = pre- and posttreatment biopsy results.

1. Patients who had either virology or biopsy data missing or both were counted as failures.

As would be anticipated from individual results for effect of treatment on eradication of HCV-RNA at end of follow-up and improvement in hepatic inflammation, the overall response rate in the INTRON® A plus ribavirin treatment group was significantly greater (<0.001), with a 10 to 14 fold improvement, than that observed in the INTRON® A plus placebo group for all methods of evaluation.

Logistic regression analysis was done on all Baseline demographic variables and disease characteristics. The only Baseline statistically significant characteristics predictive of End of Follow-up sustained response were genotype other than 1 and viral load > 2 million.

For number of viral copies (< 2 million, >2 million), the difference was statistically significant in favor of higher response rates in patients with < 2 million copies (Table 4).

When genotype and Baseline virus load are combined, a hierarchy of response is observed. Those patients with genotype other than 1 and Baseline virus load < 2 million copies had the best End of Follow-up response; those patients with genotype 1 and >2 million copies had the poorest End of Follow-up response.

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Table 4 Disease Characteristics vs Sustained Response: All-Treated Patients.

Disease Characteristic ^b	Number (%) of Patients	
	INTRON A plus ribavirin (n = 96)	INTRON A plus Placebo (n = 96)
<u>HCV-RNA/qPCR</u>		
2 million	24/36 (67)	5/29 (17)
> 2 million	26/60 (43)	0/67 (0)
<u>HCV Genotype^c</u>		
1	16/53 (30)	2/53 (4)
Other	34/43 (79)	3/19 (7)
<u>Genotype/Baseline HCV-RNA/qPCR</u>		
Other/ 2 million copies	15/16 (93)	3/14 (21)
Other/> 2 million copies	18/27 (67)	0/29 (0)
1/ 2 million copies	8/20 (40)	0/15 (0)
1/> 2 million copies	7/33 (21)	0/38 (0)

^b At entry, patients were stratified by number of viral copies (2 million, >2 million), genotype (1 or other), and cirrhosis (present or absent).

Study 2:

By basically the same methodology as described above in Study 1, a second Study 2 was also conducted. The results are summarized below.

Efficacy

The End of Follow-up overall response rate is a composite of the loss of serum HCV-RNA(qPCR) and change in liver histology at End of Follow-up (24 weeks following the end of treatment). A patient was classified as an overall responder if HCV-RNA(PCR) was negative at the 24 week posttreatment evaluation and the posttreatment Knodell HAI inflammation score (sum of categories I+II+III) had improved by 2 or more units relative to the pretreatment score. The End of Follow-up virologic response, histologic response, and overall response rates are summarized in **Tables 5, 6, and 7.**

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End of Follow-up HCV-RNA Response: Sustained Loss of HCV-RNA
24 Weeks Following the End of Treatment

The proportion of patients with eradication of HCV-RNA in the serum
24 weeks following the end of treatment was ten-fold ($p < 0.001$), in the group
of patients treated with the combination of INTRON® A plus ribavirin
compared to those receiving INTRON® A monotherapy. **Table 5** summarizes
the End of Follow-up patient response as indicated by serum HCV-RNA.

Table 5 End of Follow-up Serum HCV-RNA: Proportion of Patients with Eradication of HCV-RNA at 24 Weeks Following the End of Treatment.

Patient Response Status	Number (%) of Patients		p value
	INTRON A plus Ribavirin	INTRON A plus Placebo	
All -treated Patients	34/77 (44)	3/76 (4)	<0.001
95% Confidence Interval for each treatment:	33%-56%	0%-8%	
for difference between treatments	28%-52%		
Responders at End of Treatment ^c	34/54 (63)	3/32 (9)	

End of Follow-up Liver Histology: Improvement in Liver Histology 24
Weeks Following the End of Treatment Based on Knodell Histological Activity
Index (HAI) Scores (I+II+III)

Pre- and Posttreatment biopsies were available for 79% (61/77) of the
patients treated with INTRON® A plus ribavirin and for 84% (64/76) of those
patients who received INTRON® A plus placebo. **Table 6** summarizes the
effect of treatment on hepatic inflammation for patients with both pre- and
posttreatment liver biopsy results. As with the sustained loss of HCV-RNA
replication, the proportion of patients with improvement in liver inflammation
was significantly greater ($p < 0.001$) in patients receiving combination therapy
compared to those receiving INTRON® A monotherapy.

Table 6 End of Follow-up Liver Histology: Improvement in Liver Histology 24 Weeks Following the End of Treatment Based on the Knodell HAI (I+II+III) Score.

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Patient Status	Number (%) of Patients ^a		p value ^b
	INTRON A plus Ribavirin (n=61)	INTRON A plus Placebo (n=64)	
Improved Biopsy ^c	38(49)	27 (36)	<0.001

2. Patients with both pre-and posttreatment biopsy.

2. Fisher's Exact test.

2. Change from pretreatment to posttreatment in the Knodell Histological Index (HAI) score (sum of I+II+III) categorized as a decrease of 2 or more from pretreatment.

Overall Response

5 The overall response is summarized in **Table 7** based on the following analyses:

N. maximum likelihood estimate (MLE);

O. patients with complete data (results for both pre- and posttreatment biopsy);

10 P. patients with missing data (either or both HCV-RNA/biopsy) treated as failures.

Table 7 Overall Response Rate.

Data Analyzed	INTRON A plus Ribavirin	INTRON A plus Placebo	p value ^b
ML Estim ^a	36.5%	2.7%	<0.001
Patients with complete data ^c	25/61 (41.0%)	2/64 (3.1%)	<0.001
Treat missing as failures ^d	25/77 (32.5%)	2/76 (2.6%)	<0.001

1. MLE based on logistic regression

1. Fisher's Exact test.

1. Complete data = pre- and posttreatment biopsy results.

1. Patients who had either virology or biopsy data missing or both were counted as failures..

15 As would be anticipated from individual results for effect of treatment on eradication of HCV-RNA at End of Follow-up and improvement in hepatic inflammation, the overall response rate in the INTRON A plus ribavirin group is significantly greater ($p < 0.001$) with a 10-14 fold improvement over that

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inflammation, the overall response rate in the INTRON A plus ribavirin group is significantly greater ($p < 0.001$) with a 10-14 fold improvement over that observed with INTRON A plus placebo groups for all methods of evaluation.

5 Logistic regression analysis was done on all Baseline demographic variables and disease characteristics. The only Baseline statistically significant characteristic predictive of End of Follow-up sustained response was genotype other than 1.

10 For number of viral copies (2 million, >2 million), there was a numerical difference in favor of higher response rates in patients with 2 million copies (Table 8). When genotype and Baseline virus load are combined, a hierarchy of response is observed. Those patients with genotype other than 1 and Baseline virus load 2 million copies had the best End of Follow-up
15 response; those patients with genotype 1 and >2 million copies had the poorest End of Follow-up response.

Table 8 Disease Characteristics vs Sustained Response: All-Treated Patients.

Disease Characteristic	Number (%) of Patients	
	INTRON® A plus ribavirin (n = 77)	INTRON® A plus Placebo (n = 76)
<u>HCV-RNA/qPCR</u>		
2 million	6/9 (67)	1/12 (8)
> 2 million	28/68 (41)	2/64 (3)
<u>HCV Genotype</u>		
1	12/46 (28)	1/42 (2)
Other	21/31 (68)	2/34 (6)
<u>Genotype/Baseline HCV-RNA/qPCR</u>		
Other/ 2 million copies	4/4 (100)	0/3 (0)
Other/> 2 million copies	17/27 (62)	2/31 (6)
1/ 2 million copies	2/5 (40)	1/9 (11)
1/> 2 million copies	11/39 (28)	0/32 (0)

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way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

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CLAIMS

1. The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy.
2. The use of interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of interferon alpha in association with an effective amount of ribavirin, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy.
3. The use of both ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha, wherein the patient is one having failed to respond to a previous course of interferon alpha therapy.
4. The use as claimed in any one of Claims 1 to 3 wherein, further, the patient is a difficult to treat patient.
5. The use as claimed in Claim 4 wherein the patient is one having a viral load of greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PRC.
6. The use as claimed in Claim 4 or Claim 5 wherein the patient is one having a difficult to treat HCV genotype infection.

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7. The use as claimed in Claim 6 wherein the infection is an HCV genotype type 1 infection.
- 5 8 The use according to any one of the preceding claim wherein the interferon-alpha is selected from interferon alpha-2a, interferon alpha-2b, a consensus interferon, a purified interferon alpha product or a pegylated interferon-alpha
- 10 9. The use as claimed in any one of the preceding claims wherein the interferon alpha employed is an alpha-2b interferon.
10. The use as claimed in any one of the preceding claims wherein the amount of ribavirin administered is 400-1200 mg per day, preferably
15 800-1200 mg per day, and the amount of interferon alpha administered is from 2 to 10 million IU per week on a weekly, TIW, QOD on daily basis, more preferably 3 million IU TIW.
11. The use as claimed in any one of the preceding claims wherein
20 administration is effected for a time period of 20-30 weeks.
12. The use as claimed in Claim 11 wherein administration is further effected for a total time period of 40-50 weeks.
- 25 13. The use as claimed in Claim 11 wherein administration is further effected for a total time period of 60-80 weeks.
14. Pharmaceutical products containing ribavirin and interferon alpha in
30 separate but adjacent form.
15. Pharmaceutical products as claimed in Claim 14 wherein the interferon alpha is in a form suitable for parental injection, preferably subcutaneous injection, and the ribavirin is in a solid dosage form,

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preferably a dosage form suitable for oral administration.

- 5 16. Pharmaceutical products as claimed in Claim 14 or 15 containing an amount of ribavirin suitable for a one-day's treatment and an amount of interferon alpha suitable for at least a one-dose injection.
- 10 17. Pharmaceutical products as claimed in Claim 16 wherein the amount of ribavirin is from 400 to 1200 mg, preferably 800-1200 mg, and the amount of interferon alpha is 3 million IU, or at least 3 million IU.
- 15 18. Pharmaceutical products as claimed in any one Claims 14 to 17 in the form of a kit with instructions for combinatory use in the treatment of chronic hepatitis C infections.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/18488

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/21 //(A61K38/21,31:70)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 707 855 A (SCHERING CORPORATION) 24 April 1996 see the whole document ---	1-18
X	R. SCHVARCZ ET AL.: "COMBINATION TREATMENT WITH INTERFERON ALPHA-2b AND RIBAVIRIN FOR CHRONIC HEPATITIS C IN PATIENTS WHO HAVE FAILED TO ACHIEVE SUSTAINED RESPONSE TO INTERFERON ALONE: SWEDISH EXPERIENCE." JOURNAL OF HEPATOLOGY, vol. 23, no. SUPPL. 2, 1995, pages 17-21, XP002094474 COPENHAGEN, DK cited in the application see the whole document --- -/--	1-18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>R. SCHVARCZ ET AL.: "COMBINED TREATMENT WITH INTERFERON ALPHA-2b AND RIBAVIRIN FOR CHRONIC HEPATITIS C IN PATIENTS WITH A PREVIOUS NON-RESPONSE OR NON-SUSTAINED RESPONSE TO INTERFERON ALONE"</p> <p>JOURNAL OF MEDICAL VIROLOGY, vol. 46, no. 1, May 1995, pages 43-47, XP000600936 see the whole document</p> <p>---</p>	1-18
X	<p>J.T. BROUWER ET AL.: "WHAT OPTIONS ARE LEFT WHEN HEPATITIS C DOES NOT RESPOND TO INTERFERON? PLACEBO-CONTROLLED BENELUX MULTICENTRE RETREATMENT TRIAL ON RIBAVIRIN MONOTHERAPY VERSUS COMBINATION WITH INTERFERON."</p> <p>JOURNAL OF HEPATOLOGY, vol. 21, no. SUPPL. 1, 1994, page S17 XP002094475 COPENHAGEN, DK cited in the application * abstract nr. WP2/08 *</p> <p>---</p>	1-18
X	<p>L. CHEMELLO ET AL.: "RESPONSE TO RIBAVIRIN, TO INTERFERON AND TO A COMBINATION OF BOTH IN PATIENTS WITH CHRONIC HEPATITIS C AND ITS RELATION TO HCV GENOTYPES."</p> <p>JOURNAL OF HEPATOLOGY, vol. 21, no. SUPPL. 1, 1994, page S12 XP002094476 COPENHAGEN, DK cited in the application * abstract nr. GS5/29 *</p> <p>---</p>	1-18
X	<p>S. BRILLANTI ET AL.: "A PILOT STUDY OF COMBINATION THERAPY WITH RIBAVIRIN PLUS INTERFERON ALFA FOR INTERFERON ALFA-RESISTANT CHRONIC HEPATITIS C."</p> <p>GASTROENTEROLOGY, vol. 107, no. 3, September 1994, pages 812-817, XP000600924 see the whole document</p> <p>---</p>	1-18
X	<p>J.H. BRACONIER ET AL.: "COMBINED ALPHA-INTERFERON AND RIBAVIRIN TREATMENT IN CHRONIC HEPATITIS C: A PILOT STUDY"</p> <p>SCANDINAVIAN JOURNAL OF INFECTIOUS DISEASES, vol. 27, no. 4, 1995, pages 325-329, XP000600916 see the whole document</p> <p>-----</p>	1-18

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 707855	A	24-04-1996	
		AU 5919296 A	29-11-1996
		CA 2221314 A	21-11-1996
		CN 1190895 A	19-08-1998
		CZ 9703654 A	15-07-1998
		JP 10506640 T	30-06-1998
		NO 975309 A	19-11-1997
		PL 323477 A	30-03-1998
		WO 9636351 A	21-11-1996